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November 12, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2004D-0377; Comments on ICH Draft Guidance E14: "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs"

Dear Sir or Madam:

On behalf of our clients, The Council on Radionuclides and Radiopharmaceuticals (CORAR) and the Medical Imaging Contrast Agent Association (MICAA), we are pleased to submit these comments on the International Conference on Harmonisation's (ICH's) draft guidance E14 entitled, "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (Draft QT/QTc Guidance). 69 Fed. Reg. 55163 (Sept. 13, 2004).

CORAR and MICAA are national non-profit associations whose members manufacture and develop radiopharmaceuticals and contrast agents primarily used in medicine and life science research. Over 98% of nuclear medicine procedures and 90% of contrast-enhanced procedures performed in the United States are done with products manufactured by CORAR and MICAA members, respectively.

As explained below, CORAR and MICAA generally agree with the Draft QT/QTc Guidance's approach to evaluation of QT/QTc interval prolongation and requests that

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medical imaging drugs be cited as a specific example of new drugs which would not typically be required to undergo a "thorough QT/QTc study." In addition, with regard to whether non-clinical data are sufficient to preclude risk of QT/QTc prolongation, we urge the Agency to revise the guidance so that it applies uniformly across all regions.

I. MEDICAL IMAGING DRUGS TYPICALLY DO NOT REQUIRE A THOROUGH QT/QTc STUDY

A. Background

The potential for pharmaceutical products to delay cardiac repolarization and lead to serious and sometimes fatal cardiac arrhythmias was brought to light after the antihistamine Seldane® (terfenadine), when taken with certain other medications or by patients with liver disease, was implicated in several sudden cardiac arrhythmia deaths. This and other similar events brought greater regulatory focus on the evaluation of QT and QTc interval prolongation – markers for delayed repolarization – in various phases of clinical investigation based on signals of such prolongation in earlier stages of development. CORAR and MICAA support ICH's and the U.S. Food and Drug Administration's (FDA's) role in protecting the public health from products that can prolong the QT/QTc interval when supratherapeutic doses are reached.

As noted in the Draft QT/QTc Guidance, QT/QTc interval prolongation in problematic cases has led to regulatory action including market withdrawal, relegation to second line status in the labeling, and denial of approval for various drug products. The affected drugs, however, all share several common features that amplify the potential for overdosing: they are intended for chronic administration, are self-dosed by patients and are administered in non-healthcare settings. Many are also metabolized by the cytochrome P450 enzyme system that, when inhibited by other agents, can lead to excessive blood levels. As was the case with Seldane®, this combination of factors brings about the potential for supratherapeutic dose levels, and therefore exacerbated proarrhythmic adverse events, in a setting where urgent care may not be readily accessible.

In recognition of these factors, the Draft QT/QTc Guidance limits its own applicability to new drugs with systemic bioavailability and appropriately notes that, "[t]he investigational approach used for a particular drug should be individualized, depending on the pharmacodynamic, pharmacokinetic, and safety characteristics of the product, as well as

on its proposed clinical use."[1] Therefore, while a "thorough QT/QTc study" would be required in many cases, the Draft QT/QTc Guidance provides that certain additional factors such as "duration of treatment, metabolic profile, pharmacodynamic duration of action, and previous experience with other members of the same chemical or pharmacological class" could influence the need for such a study.[2]

As discussed below, medical imaging drugs present with most of these factors and, accordingly, CORAR and MICAA believe that a new medical imaging drug would not ordinarily be required to undergo a "thorough QT/QTc study" as described in Section 2.1.2 of the Draft QT/QTc Guidance. The unique pharmacodynamic and use profiles of medical imaging drugs act as an intrinsic risk management program against supratherapeutic blood levels and resultant QT interval prolongation. These special characteristics are already taken into account in non-QT related developmental efforts as demonstrated by the scope of the FDA's series of guidances on Developing Medical Imaging Drugs and Biological Products.[3]

B. Duration of Treatment

Medical imaging drugs, unlike most other drug products, are typically administered in single doses, limiting systemic availability and drug accumulation. Unlike chronic use drugs and even some acute use products that are given over several weeks, the potential for systemic accumulation which could lead to QT interval prolongation is not present.

C. Metabolic Profile

Most radiopharmaceuticals and contrast agents have very short half lives and are excreted rapidly (less than 24-72 hours post-dose). Thus, they reach their maximum concentration rapidly and never achieve steady state drug concentration, further diminishing the likelihood of producing supratherapeutic drug exposure through interaction with other drug products or physiologic conditions. In addition, many

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1 Draft QT/QTc Guidance at 3-4.

2 Id. at 4.

3 FDA Guidances for Industry: Developing Medical Imaging Drugs and Biological Products: Part 1: Conducting Safety Assessments; Part 2: Clinical Indications; Part 3: Design, Analysis, and Interpretation of Clinical Studies (June 17, 2004).

radiopharmaceuticals and contrast agents are eliminated without a metabolic step, and we are unaware of any such products that induce or inhibit the P450 enzyme system in metabolism. As a result, the risk of extreme (supratherapeutic) blood levels being reached through inhibition of drug metabolism by concomitant medications or food is unlikely for medical imaging products, and clinical testing of maximum achievable dose by coadministration with metabolic inhibitors is rendered irrelevant.

D. Pharmacodynamic Duration of Action

Medical imaging drugs are designed to aid in diagnosis or monitoring of disease through enhanced visualization of anatomic structures and physiologic processes. These agents are designed to have an effect on various imaging modalities and do not typically bring about a significant pharmacologic response. Unlike Seldane® and other drug products associated with QT side effects, medical imaging drugs are not administered to achieve a systemic steady state.

Radiopharmaceuticals, in particular, are typically administered in very low mass doses at which dose-related adverse events such as QT interval prolongation are unlikely to occur. Administered doses for radiopharmaceuticals are typically so low as to be undetectable in the systemic circulation. In fact, bioequivalence of radiopharmaceutical products is typically established using efficacy (imaging capability) rather than pharmacokinetic data.

E. Use Profile

In addition to the factors listed in the Draft QT/QTc Guidance, medical imaging drugs also have a unique use profile which should be considered in determining whether a "thorough QT/QTc study" is necessary. Unlike most other prescription drugs, radiopharmaceuticals and contrast agents are uniformly administered by trained personnel in a highly supervised healthcare setting. They are not self-administered and are used exclusively in hospitals and diagnostic imaging clinics. The medical personnel administering the drug are either physicians or specially trained medical technologists. In addition, these drugs are typically prepared in single-dose or two dose-unit vials, further substantially minimizing the possibility of overdosing. The entire product is typically administered by injection in less than 30 seconds, with a medical professional present during the entire administration.

This use profile, combined with the duration of treatment, metabolic profile, and pharmacodynamic duration of action discussed above, renders repolarization-associated

cardiac arrhythmias for medical imaging agents very improbable. However, in the unlikely event of such an occurrence, urgent care is readily available. In addition to the trained medical personnel available at the imaging center itself, such centers are typically in close proximity to tertiary care or university medical center setups, due to the cost of running an imaging center. Thus, appropriate emergency medical attention is within quick reach should any serious adverse event occur.

F. Summary

In summary, the special characteristics of radiopharmaceuticals and contrast agents render it highly unlikely that they would lead to clinically significant cardiac arrhythmias. CORAR and MICAA agree with the Draft QT/QTc Guidance's conclusion that the need for a "thorough QT/QTc study" depends on duration of treatment, metabolic profile, and pharmacodynamic duration of action. Based on these factors, detailed evaluation of the effects of medical imaging drugs on QT/QTc interval prolongation in a "thorough QT/QTc study" is not warranted in most cases. In the absence of a positive signal regarding QT/QTc interval prolongation in preclinical studies (conducted in accordance with ICH S7B), the investigation of products with these characteristics need not intensively monitor for QT/QTc interval prolongation as described in Section 2.1.2 of the Draft QT/QTc Guidance. Instead routine ECG monitoring and analyses conducted during the drug's development should provide sufficient management of risk for these products. We request that the guidance clarify this point by specifically identifying medical imaging drugs as an example of a class of drugs for which a "thorough QT/QTc study" would not ordinarily be necessary. This could be done by adding the following sentence at the end of the first paragraph of Section 2.1 (page 4, line 165):

> "For example, medical imaging drugs (particularly radiopharmaceuticals) are an example of a class of drugs which, because they are generally administered in single doses, are excreted rapidly, and typically do not bring about a significant pharmacological response, would ordinarily not require a thorough QT/QTc study in the absence of a pre-clinical signal."

II. GUIDANCE ON THE ROLE OF NON-CLINICAL DATA SHOULD BE UNIFORM ACROSS ALL REGIONS

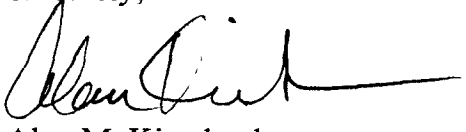
Section 2.1 of the Draft QT/QTc Guidance explains that the sufficiency of non-clinical testing to preclude clinical risk of QT/QTc prolongation is controversial. The Guidance therefore provides that a thorough QT/QTc study would generally be required in regions where non-clinical data are not considered sufficient to preclude such risk, but the guidance could be modified in regions where non-clinical data are considered sufficiently informative about such risk.

Under the Draft Guidance, the same drug might require extensive clinical evaluation of QT/QTc interval prolongation in one country but limited evaluation in another. Permitting regional variations on this point defeats the primary purpose of the ICH: the global standardization of requirements for drug registration. We urge that this section of the Draft Guidance be revised so that the same requirements apply globally, rather than being a matter for regional interpretation.

* * *

We appreciate your consideration of these comments as you work to finalize the ICH guidance on clinical evaluation of QT/QTc interval prolongation.

Sincerely,



Alan M. Kirschenbaum

AMK/vam

cc: George Mills, M.D. (HFD-160)